MICROCAPSULES OF PREDETERMINED PEPTIDE(S) SPECIFICITY (IES), THEIR PREPARATION AND USES

BACKGROUND OF THE INVENTION

1. Field of the Invention

This invention relates to the field of in vivo delivery of active agents. More particularly, this invention relates to microcapsules prepared by the reaction of Lewis acid and base wall-forming reactants, targeted for the delivery of encapsulated ingredient(s).

2. Description of the Background

Microcapsules are fine dispersions of solids or droplets of liquid onto which a thin film coating has been applied. The average diameter of microcapsules may vary from one micron to several hundred microns depending on the materials used and their method of production. The term nanocapsule is usually applied to similar constructs having average diameters of less than one micron. Microspheres can be differentiated over microcapsules in that they do not possess distinct core and coating regions, but have the ingredient(s) to be delivered and adjuvant, if present, uniformly distributed throughout the bulk of the particle. The term microparticle is often used to describe constructs which cannot be readily placed into either of the above two categories or as a generic term for both. If the constructs are less than one micron in diameter, then the corresponding terms nanosphere and nanoparticle are often utilized.

Microencapsulation is a process by which a relatively thin coating can be applied to dispersions of small particles of solids or droplets of liquids. This process provides a means for converting liquids to solids, and for altering colloidal and surface properties while avoiding environmental damage, and controlling the release characteristics or availability of coated materials. Several of these properties can be attained by macropackaging techniques. The uniqueness of microencapsulation, however, resides in the smallness of the resulting coated particles, and their subsequent adaptation to a wide variety of dosage forms and use in multiple product applications. Up to the present time, known methods for producing microcapsules on an industrial scale have often involved the use of organic solvents, even though the use of the latter may present environmental and safety problems, and their removal is often difficult and, if incomplete, leaves organic contaminants.

In U.S. Pat. No. 3,137,631 water-insoluble organic liquids are encapsulated by cross-linking synthetic resins with the aid of heat or catalysts, or both. The capsule shells are described as formed from covalently linked non-ionic materials or from heat denaturable proteins, while the cross-linking is said to stabilize the resulting capsules. U.S. Pat. No. 4,205,060 discloses microcapsules comprising a core containing a water-soluble salt formed from polymeric ionic resin and a medicament. The medicament salt is formed either by reaction of an acidic polymer with a basic medicament or, a basic polymer with an acidic drug. The walls of the microcapsules are formed from water-insoluble film-forming polymers. The film-forming polymers identified as suitable sheathing agents are all water-insoluble, neutral, non-ionized polymers. The capsules of the prior patent are made by preparing an aqueous solution of a salt made by reacting a medicament and a core polymer, placing a water-insoluble sheath-forming polymer in a first water-immiscible organic liquid, dispersing the aqueous solution in the organic solution, and adding to the dispersion a second water-immiscible liquid, which does not act as a solvent for the sheath-forming polymer, to precipitate the film around droplets of the dispersed aqueous phase.

In U.S. Pat. No. 4,606,940, microcapsules are prepared by coacervation and precipitation of the encapsulating material with the aid of temperature changes. A single colloid is dispersed in water and the water of solvation is removed from the colloid by addition of chemical compounds having greater affinity for water than the colloid, causing the colloid chains to come closer together and form a coacervate. U.S. Pat. No. 3,959,457 to Speaker et al. forms microcapsules by reacting in a low boiling point, polar, organic solvent, a finely dispersed emulsion, a water-immiscible solution of an organic polyfunctional Lewis base, and an aqueous solution of a partially hydrophilic, partially lipophilic, polyfunctional Lewis acid. These capsules have lipophilic cores and carry pharmaceuticals, such as quinacrine. A modification of the technology disclosed in U.S. Pat. No. 3,959,457, is described in U.S. Pat. No. 5,132,117, where a lipophilic surfactant, such as sorbitan trioleate is added to the organic phase prior to emulsification, causing an inversion of the two phases. Thus, the aqueous phase becomes encapsulated while the organic phase remains outside the microcapsules as a continuous phase.

Yet another method of producing microcapsules introduced droplets of an aqueous anionic polymer, such as sodium carboxymethylcellulose, and a material to be encapsulated, into an aqueous alkylamine salt, such as stearylamine hydrochloride. The reagents react at the droplet boundary to form a water-insoluble wall, the size of which may be varied by varying the size of the polymer solution droplets. The film forming the wall is formed at a "pseudo-interface" between the two aqueous solutions.

Belgium Patent No. 882,476 to Lim, describes the formation of calcium alginate microspheres, surface-treating them to form polylysine or polyethylenimine alginate coacervates, and then core-liquifying them with a calcium chelating agent. U.S. Pat. No. 4,744,933 to Rha & Rodrigues-Sanchez simplifies the Lim process by spraying one charged polymer directly into an oppositely charged polymer to produce a complex coacervate thereby obtaining a similar product. U.K. Patent Application 2,135,954A by Dautzenberg et al. discloses the formation of complex coacervate microcapsules by causing anionic polymer solution droplets to fall into solutions of oppositely charged poly-quaternary ammonium salts.

Many of the previously known entirely aqueous systems were based on the formation of coacervates, and provide microbeads of widely ranging particle size. Some require strongly acidic media, e.g., pH 3–4, to precipitate proteinaceous coacervates. More complex coacervates precipitate from aqueous solution of two oppositely charged polymers. Hydrogels based on aqueous hydroxyethylacrylate involve free radical polymerization, catalyzed by peroxy species or ionizing radiation, which may be destructive of fragile protein molecules or intact organisms, but suitable for delivery of other materials (Andrade, et al, Trans. Amer. Soc. Artif. Int. Organs 17:222–228 (1971)). Alginic acid and calcium ion hydrogels may be formed by a process that is suitable for enveloping both microbes and multicellular organisms such as nematodes (Lim & Sun, Science 210:908–910 (1980)).

Most microparticulate delivery systems available are not surface modified. In consequence, their particles, when used for imaging or delivering therapeutic agents, are rapidly engulfed by the reticuloendothelial system. For example, albumin or galactose microspheres have been employed for imaging purposes. These microspheres are cleared from blood in about 20 seconds. Polyoxyethylene esters linked to the surface of polylactide-coglycolide microspheres are